

CLAIMS

1. A crystal of a dipeptidyl peptidase IV, having characteristics sufficient to ensure a resolution capable of analyzing its three-dimensional structure up to the side chain level by X-ray crystallographic structural analysis.

2. The crystal according to claim 1, wherein the dipeptidyl peptidase IV is a soluble polypeptide comprising a region located at extramembrane in a full-length human dipeptidyl peptidase IV.

3. The crystal according to claim 1 or 2, wherein the dipeptidyl peptidase IV is a polypeptide having an amino acid sequence in which a transmembrane region is deleted from the amino acid sequence of SEQ ID NO: 2, and a tag peptide is optionally added to a C-terminal side or N-terminal side thereof.

4. The crystal according to any one of claims 1 to 3, wherein the crystal has a space group of $P2_12_12_1$, and a lattice constant of the unit cell of $|a| = 118.0 \pm 5.0 \text{ \AA}$, $|b| = 125.9 \pm 5.0 \text{ \AA}$, $|c| = 136.8 \pm 5.0 \text{ \AA}$, and $\alpha = \beta = \gamma = 90^\circ$, and is orthorhombic.

5. The crystal according to any one of claims 1 to 4, wherein the crystal has the structural coordinate shown in Figure 4.

6. The crystal according to any one of claims 1 to 4, wherein the crystal has a structural coordinate different from the structural coordinate as shown in

Figure 4 via fluctuation of a protein.

7. A three-dimensional structural coordinate of a dipeptidyl peptidase IV, comprising the structural coordinate shown in Figure 4.

8. A three-dimensional structural coordinate of a dipeptidyl peptidase IV, comprising a structural coordinate different from the structural coordinate as shown in Figure 4 via fluctuation of a protein.

9. The three-dimensional structural coordinate according to claim 8, wherein the fluctuation of a protein is a state that is caused by molecular oscillation or temperature, and exhibits an activity for the dipeptidyl peptidase IV in a living body.

10. The three-dimensional structural coordinate according to any one of claims 7 to 9, wherein the dipeptidyl peptidase IV is a soluble polypeptide comprising a region located at extramembrane in a full-length human dipeptidyl peptidase IV.

11. The three-dimensional structural coordinate according to any one of claims 7 to 10, wherein the dipeptidyl peptidase IV is a polypeptide having an amino acid sequence in which a transmembrane region is deleted from the amino acid sequence of SEQ ID NO: 2, and a tag peptide is optionally added of to a C-terminal side or N-terminal side thereof.

12. A three-dimensional structural coordinate of a region in a dipeptidyl peptidase IV, comprising the three-dimensional structural coordinate of the region selected from the group consisting of the following (a) to (d):

- 5 (a) a region characterized by Ser 630, Asp 708 and His 740 in the amino acid sequence of SEQ ID NO: 2, and
all or a part of a group of the amino acid residues located in the adjacent area of each of the Ser 630, Asp 708 and His 740 in the structural coordinate shown in Figure 4 or the three-dimensional structure model defined by the structural coordinate;
- 10 (b) a region characterized by Ser 630, Asp 708 and His 740 in the amino acid sequence of SEQ ID NO: 2, and
all or a part of a group of the amino acid residues comprising amino acids capable of maintaining physicochemical characteristics physiologically equivalent to each of amino acids in the group of the amino acid residues
15 located in the adjacent area of each of Ser 630, Asp 708 and His 740, in the structural coordinate shown in Figure 4 or the three-dimensional structure model defined by the structural coordinate,
- (c) a region characterized by a group of amino acid residues comprising amino acids capable of maintaining physicochemical characteristics
20 physiologically equivalent to each of Ser 630, Asp 708 and His 740 in the amino acid sequence of SEQ ID NO: 2, and
all or a part of a group of the amino acid residues located adjacent area of said group of the amino acid residues in the structural coordinate shown in Figure 4 or the three-dimensional structure model defined by the structural
25 coordinate; and

(d a region characterized by a group of amino acid residues comprising amino acids capable of maintaining physicochemical characteristics physiologically equivalent to each of Ser 630, Asp 708 and His 740 in the amino acid sequence of SEQ ID NO: 2, and

5 all or a part of a group of amino acid residues comprising amino acids capable of maintaining physicochemical characteristics physiologically equivalent to each of the amino acids in the group of the amino acid residues located in the adjacent area of said group of the amino acids, in the structural coordinate shown in Figure 4 or the three-dimensional
10 structure model defined by the structural coordinate,

wherein the region in the dipeptidyl peptidase IV is a region involved in binding or interaction between the dipeptidyl peptidase IV and an effector of the dipeptidyl peptidase IV.

15 13. The three-dimensional coordinate according to claim 12, wherein the physicochemical characteristic is selected from the group consisting of features in shape of a three-dimensional structure, hydrophobicity, electric charge and pK.

14. A method for obtaining a three-dimensional coordinate of a homolog
20 protein of a dipeptidyl peptidase IV, characterized in refining an electron density map of the homolog protein of the dipeptidyl peptidase IV comprising the amino acid sequence of SEQ ID NO: 2, based on all and/or a part of the three-dimensional coordinate of any one of claims 7 to 13, to give a three-dimensional structural coordinate.

15. A method for obtaining a three-dimensional structural coordinate of a crystal of a complex of a dipeptidyl peptidase IV and an effector of the dipeptidyl peptidase IV characterized in using all and/or a part of the three-dimensional structural coordinate of any one of claims 7 to 13, to give a three-dimensional structural coordinate.
16. A method for identifying pharmacophore of an effector of the dipeptidyl peptidase IV, characterized in identifying the pharmacophore based on all and/or a part of the three-dimensional structural coordinate of any one of claims 7 to 13, and the steric conformation of the effector of the dipeptidyl peptidase IV.
17. A method for designing, identifying, evaluating or searching an effector of a dipeptidyl peptidase IV, characterized in designing, identifying, evaluating or searching a compound capable of acting on the dipeptidyl peptidase IV, based on all and/or a part of the three-dimensional structural coordinate of any one of claims 7 to 13.
18. The method according to claim 17, wherein the method for designing, identifying, evaluating or searching an effector comprises the steps of:
- (i) identifying a region to be targeted for binding or interaction with the effector in a dipeptidyl peptidase IV, based on all and/or a part of the three-dimensional structural coordinate according to any one of claims 7 to 13 and the steric conformation of the effector of the dipeptidyl peptidase IV;
 - (ii) identifying atoms or atomic groups capable of generating in the above

- region at least one intermolecular interaction selected from the group consisting of covalent bond, ionic interaction, ion-dipole interaction, dipole-dipole interaction, hydrogen bonding, van der Waals force, electrostatic interaction and hydrophobic interaction, with the atoms or atomic groups existing in a candidate compound; and
- (iii) designing a compound based on the information of the above step (i) and/or (ii).

19. The method according to claim 18, wherein the method further comprises the steps of:

detecting an interaction between the dipeptidyl peptidase IV and the designed, identified, evaluated or searched candidate compound, wherein when an interaction is detected, the candidate compound is identified as a compound capable of binding to the dipeptidyl peptidase IV, based on a degree of the interaction as an index.

20. The method according to claim 18 or 19, wherein the method further comprises the steps of:

contacting the dipeptidyl peptidase IV with the designed, identified, evaluated or searched candidate compound and measuring an activity of the dipeptidyl peptidase IV, wherein when an activity increases or decreases, the designed, identified, evaluated or searched candidate compound is identified as a compound having enhancing action or inhibitory action on the activity of the dipeptidyl peptidase IV, based on a degree of the increase or decrease as an index.

21. An effector of the dipeptidyl peptidase IV obtainable by the method of any one of claims 17 to 20.
- 5 22. A program and a medium therefor for use of the three-dimensional structural coordinate of any one of claims 7 to 13, wherein all and/or a part of the three-dimensional structural coordinate of any one of claims 7 to 13 is recorded.
- 10 23. The program and the medium according to claim 22, comprising a means for identifying, searching, evaluating or designing a compound capable of binding to the dipeptidyl peptidase IV or a compound having an enhancing action or inhibitory action on the activity for the dipeptidyl peptidase IV.
- 15 24. The program and the medium according to claim 23, further comprising a means for displaying a three-dimensional graphic display of a molecule.